HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RYZODEG 70/30 safely and effectively. See full prescribing information for RYZODEG 70/30.

RYZODEG® 70/30 (insulin degludec and insulin aspart injection), for subcutaneous use
Initial U.S. Approval: 2015

---------- RECENT MAJOR CHANGES----------
Indications and Usage (1) 12/2016

----------INDICATIONS AND USAGE----------
RYZODEG 70/30 is a mixture of insulin degludec, a long-acting human insulin analog, and insulin aspart, a rapid-acting human insulin analog, indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus (1).

Limitations of Use:
Not recommended for treating diabetic ketoacidosis.
Not recommended for pediatric patients requiring less than 5 units.

----------DOSAGE AND ADMINISTRATION----------
- DO NOT dilute or mix RYZODEG 70/30 with any other insulin products or solutions (2.1).
- Rotate injection sites to reduce the risk of lipodystrophy (2.1).
- Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goal. (2.2, 2.3, 2.4, 2.5).
- Administer subcutaneously once or twice daily with any main meal (s) (2.2).
- Administer a rapid- or short-acting insulin at other meals if needed (2.2).
- Patients with type 1 diabetes will generally require a rapid-or short-acting insulin at meals when RYZODEG 70/30 is not administered (2.2).
- Adjust the dose according to fasting blood glucose measurements (2.2).
- The recommended time between dose increases is 3 to 4 days (2.2)
- Converting from other insulin therapies may require adjustment of timing and dose of RYZODEG 70/30 (2.4, 2.5).

----------DOSAGE FORMS AND STRENGTHS----------
RYZODEG 70/30 100 units/mL (U-100) available in:
- 3 mL FlexTouch® (3).

----------CONTRAINDICATIONS----------
- During episodes of hypoglycemia (4).
- Hypersensitivity to RYZODEG 70/30 or one of its excipients (4).

----------WARNINGS AND PRECAUTIONS----------
- *Never share* a RYZODEG 70/30 FlexTouch pen between patients, even if the needle is changed (5.1).
- *Hyper- or hypoglycemia with changes in insulin regimen:* Carry out under close medical supervision and increase frequency of blood glucose monitoring (5.2).
- *Hypoglycemia:* May be life-threatening. Increase monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness (5.3,5.4, 6.1).
- *Hypoglycemia due to medication errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. DO NOT transfer RYZODEG 70/30 into a syringe for administration as overdosage and severe hypoglycemia can result (5.4).
- *Hypersensitivity reactions*: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue RYZODEG 70/30, monitor and treat if indicated (5.5).
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated (5.6).
- *Fluid retention and heart failure with concomitant use of Thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs (5.7).

----------ADVERSE REACTIONS----------
Adverse reactions commonly associated with RYZODEG 70/30 are:
- hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at (1-800-727-6500) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- *Drugs that affect glucose metabolism:* Adjustment of insulin dosage may be needed; closely monitor blood glucose (7).
- *Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Signs and symptoms of hypoglycemia may be reduced or absent (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RYZODEG 70/30 is indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus.

Limitations of Use

- Not recommended for the treatment of diabetic ketoacidosis.
- Not recommended for pediatric patients requiring less than 5 units of RYZODEG 70/30 daily.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check insulin label before administration *[see Warnings and Precautions (5.4)]*.
- Inspect visually for particulate matter and discoloration. Only use RYZODEG 70/30 if the solution appears clear and colorless.
- Train patients on proper use and injection technique before initiating RYZODEG 70/30. Training reduces the risk of administration errors such as needle sticks and incomplete dosing.
- Inject RYZODEG 70/30 subcutaneously into the thigh, upper arm, or abdomen.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions (6.1)]*.
- DO NOT administer RYZODEG 70/30 intravenously, intramuscularly, or in an insulin infusion pump.
- DO NOT dilute or mix RYZODEG 70/30 with any other insulin products or solutions.

2.2 General Dosing Instructions

- In adults, inject RYZODEG 70/30 subcutaneously once or twice daily with any main meal and in pediatric patients once daily with any main meal.
- Administer a rapid- or a short-acting insulin at other meals if needed.
- Patients with type 1 diabetes will generally require a rapid- or short-acting insulin at meals when RYZODEG 70/30 is not administered for optimal glucose control.
- Individualize and titrate the dose of RYZODEG 70/30 based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal *[see Warnings and Precautions (5.2)]*.
- Adjust the RYZODEG 70/30 dose according to blood glucose measurements before breakfast (fasting).
- The recommended time between dose increases is 3 to 4 days.
- Dose adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia *[see Warnings and Precautions (5.3)]*.

- If a dose of RYZODEG 70/30 is missed, the next dose should be taken with the next main meal of that day and thereafter resume the usual dosing schedule. Patients should not take an extra dose to make up for a missed dose.

2.3 Starting Dose in Insulin-Naïve Patients

Type 1 Diabetes Mellitus

The recommended starting dose of RYZODEG 70/30 in insulin-naïve patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be administered as a short- or rapid-acting insulin divided between each daily meal. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin-naïve patients with type 1 diabetes.

Type 2 Diabetes Mellitus

The recommended starting dose of RYZODEG 70/30 in insulin-naïve patients with type 2 diabetes mellitus is 10 units once daily.

2.4 Starting Dose in Patients with Type 1 or Type 2 Diabetes on a Once or Twice Daily Premix or Self-mix Insulin Alone or as Part of a Regimen of Multiple Daily Injections

Adults with Type 1 or Type 2 Diabetes

Start RYZODEG 70/30 at the same unit dose and injection schedule as the premix or self-mix insulin. In patients also using short- or rapid-acting insulin at mealtimes continue the short- or rapid-acting insulin at the same dose for meals NOT covered by RYZODEG 70/30.

Pediatric Patients 1 Year of Age and Older with Type 1 or Type 2 Diabetes

Start RYZODEG 70/30 at 80% of the total daily mixed insulin dose in order to minimize the risk of hypoglycemia *[see Warnings and Precautions (5.2)]* and administer once daily with the main meal of the day. In patients also using short- or rapid-acting insulin at mealtimes continue the short- or rapid-acting insulin at the same dose for meals NOT covered by RYZODEG 70/30.

2.5 Starting Dose in Patients with Type 1 or Type 2 Diabetes on a Once or Twice Daily Basal Insulin Alone or as Part of a Regimen of Multiple Daily Injections

Adults with Type 1 or Type 2 Diabetes

In patients with type 2 diabetes switching from a regimen that includes only a once- or twice-daily basal insulin, start RYZODEG 70/30 at the same unit dose and injection schedule. For patients switching from once-daily basal insulin to once-daily RYZODEG

70/30, monitor blood glucose after starting therapy due to the rapid-acting insulin component *[see Warnings and Precautions (5.2)]*.

In patients switching from a multiple daily injections regimen that includes a basal and short- or rapid-acting insulin at mealtimes, start RYZODEG 70/30 once daily with the main meal at the same unit dose as the basal insulin. Continue the short- or rapid-acting insulin at the same dose for meals NOT covered by RYZODEG 70/30.

Pediatric Patients 1 Year of Age and Older with Type 1 or Type 2 Diabetes

Start RYZODEG 70/30 at 80% of the long- or intermediate-acting insulin component of the daily regimen in order to minimize the risk of hypoglycemia *[see Warnings and Precautions (5.2)]* and administer once daily with the main meal of the day. In patients also using short- or rapid-acting insulin at mealtimes continue the short- or rapid-acting insulin at the same dose for meals NOT covered by RYZODEG 70/30.

3 DOSAGE FORMS AND STRENGTHS

RYZODEG 70/30 is available as a clear and colorless solution for injection in:

- 100 units/mL (U-100): 3 mL FlexTouch disposable prefilled pen

4 CONTRAINDICATIONS

RYZODEG 70/30 is contraindicated:

- During episodes of hypoglycemia *[see Warnings and Precautions (5.3)]*.
- In patients with hypersensitivity to RYZODEG 70/30 or one of its excipients *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a RYZODEG 70/30 FlexTouch Pen Between Patients

RYZODEG 70/30 FlexTouch disposable prefilled pen should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, adjustments in concomitant oral anti-diabetic treatment may be needed. When converting from other insulin therapies to RYZODEG 70/30 follow dosing recommendations *[see Dosage and Administration (2.4, 2.5)]*.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of insulin, including RYZODEG 70/30 *[see Adverse Reactions (6.1)]*. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or

operating other machinery). RYZODEG 70/30, or any insulin, should not be used during episodes of hypoglycemia *[see Contraindications (4)]*.

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) *[see Drug Interactions (7)]*, or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia generally increases with intensity of glycemic control. The risk of hypoglycemia after an injection is related to the duration of action of the insulin *[see Clinical Pharmacology (12.2)]* and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of RYZODEG 70/30 may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature.

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication *[see Drug Interactions (7)]*. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations (8.6, 8.7)]*.

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between insulin products have been reported. To avoid medication errors between RYZODEG 70/30 and other insulins, instruct patients to always check the insulin label before each injection.

Do not transfer RYZODEG 70/30 from the RYZODEG 70/30 pen to a syringe. The markings on the insulin syringe will not measure the dose correctly and can result in overdosage and severe hypoglycemia *[see Dosage and Administration (2.1) and Warnings and Precautions (5.3)]*.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including RYZODEG 70/30. If hypersensitivity reactions occur, discontinue RYZODEG 70/30; treat per standard of care and monitor until symptoms and signs resolve. RYZODEG 70/30 is contraindicated in patients who have had hypersensitivity reactions to insulin degludec, insulin aspart, or one of the excipients *[see Contraindications (4)]*.

5.6 Hypokalemia

All insulin products, including RYZODEG 70/30, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to potassium concentrations).

5.7 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR Gamma Agonist

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists can cause dose related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with insulin, including RYZODEG 70/30 and a PPAR-gamma agonist should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Hypersensitivity and allergic reactions *[see Warnings and Precautions (5.5)]*
- Hypokalemia *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of RYZODEG 70/30 in subjects with type 1 diabetes or type 2 diabetes was evaluated in five trials of 6-12 month duration in adults and in one trial of 16 week duration in pediatric patients 1 year of age and older with type 1 diabetes *[see Clinical Studies (14)]*.

The data in Table 1 reflect the exposure of 362 adults with type 1 diabetes to RYZODEG 70/30, with a mean exposure duration to RYZODEG 70/30 of 43 weeks. The mean age was 41 years and 1% were older than 75 years. Fifty-two percent were male, 91% were White, 3% were Black or African American and 3% were Hispanic. The mean body mass index (BMI) was 26 kg/m^2. The mean duration of diabetes was 17 years and the mean HbA_{1c} at baseline was 8.3%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 19%, 25%, 6% and 4% respectively. The mean eGFR at baseline was 88 mL/min/1.73 m^2 and 6% of patients had an eGFR less than 60 mL/min/1.73 m^2.

The data in Table 2 reflect the exposure of 998 adults with type 2 diabetes to RYZODEG 70/30 with a mean exposure duration to RYZODEG 70/30 of 24 weeks. The mean age was 58 years and 3% were older than 75 years. Fifty-four percent were male, 44% were White, 4% were Black or African American and 6% were Hispanic. The mean BMI was 29 kg/m^2. The mean duration

of diabetes was 12 years and the mean HbA_{1c} at baseline was 8.5%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported for 15%, 21%, 10% and 1% respectively. At baseline, the mean eGFR was 84 mL/min/1.73 m^2 and 11% of patients had an eGFR less than 60 mL/min/1.73 m^2.

Common adverse reactions (excluding hypoglycemia) occurring in RYZODEG 70/30-treated subjects during clinical trials in adult patients with type 1 diabetes mellitus and adults with type 2 diabetes mellitus are listed in Tables 1 and 2, respectively. Common adverse reactions were defined as reactions occurring in ≥5% of the population studied. Hypoglycemia is not shown in these tables but discussed in a dedicated subsection below.

181 pediatric patients 1 year of age and older with type 1 diabetes were exposed to RYZODEG 70/30 with a mean exposure duration to RYZODEG 70/30 of 16 weeks. The mean age was 10.5 years: 22.5% were ages 1-5 years, 33.5% were ages 6-11 years, and 44% were ages 12-17 years. 48.9% were male, 92.9% were White, 4.4% were Black or African American and 8.2% were Hispanic. The mean body mass index (BMI) was 19.2 kg/m^2. The mean duration of diabetes was 4.4 years and the mean HbA_{1c} at baseline was 8.1%. A history of neuropathy and nephropathy at baseline was reported in 2.2% and 0.5%, respectively. Common adverse reactions in RYZODEG 70/30 treated children with type 1 diabetes mellitus were similar to the adverse reactions listed in Table 1.

Table 1: Adverse Reactions Occurring in ≥5% of RYZODEG 70/30-Treated Adult Patients with Type 1 Diabetes Mellitus

Adverse Reaction	**RYZODEG 70/30 (N=362)**
Nasopharyngitis	24.6%
Headache	9.7%
Upper respiratory tract infection	9.1%
Influenza	6.9%

Table 2: Adverse Reactions Occurring in ≥5% of RYZODEG 70/30-Treated Adult Patients with Type 2 Diabetes Mellitus

Adverse Reaction	**RYZODEG 70/30 (N=998)**
Nasopharyngitis	11.1%
Upper respiratory tract infection	5.7%
Headache	5.6%

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including RYZODEG 70/30 *[see Warnings and Precautions (5.3)]*. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose,

intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for RYZODEG 70/30 with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that occur in clinical practice.

Rates of hypoglycemia by trial are shown in Table 3 for type 1 diabetes in adult and pediatric patients and Table 4 for type 2 diabetes in adults treated with RYZODEG 70/30 *[see Clinical Studies (14)]*. Severe hypoglycemia in trials with adult patients was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycemia in the pediatric trial was defined as an altered mental status where the child could not assist in his own care, was semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or intravenous glucose).

A Novo Nordisk hypoglycemia episode was defined as a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Table 3: Percent (%) of Patients with Type 1 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia[§] on RYZODEG 70/30 in Adult and Pediatric Clinical Trials

	Study A **RYZODEG 70/30 OD* + Insulin Aspart BID****, **Adults** **52 weeks** **(N= 362)**	**Study F** **RYZODEG 70/30 OD* + Insulin Aspart TID*****, **Pediatrics** **16 weeks** **(N= 181)**
Severe hypoglycemia[±]		
Percent of patients	13.3%	6.1%
Novo Nordisk hypoglycemia[§]		
Percent of patients	95.0%	92.8%

*OD: once daily
**BID: twice daily
***TID: three times daily
[±]Severe hypoglycemia in pediatric patients: an episode with altered mental status, where the child could not assist in his own care, was semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or intravenous glucose).
[§]Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Table 4: Percent (%) of Patients with Type 2 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia[§] on RYZODEG 70/30 in Adult Clinical Trials

	Study B RYZODEG 70/30 OD* insulin naïve, previously on 2 or more OADs*** (N=265)	Study C RYZODEG 70/30 OD* previously on basal insulin OD and 1 or more OADs*** (N=230)	Study D RYZODEG 70/30 BID** previously on OD*/BID premix/self-mix, ±OADs*** (N=224)	Study E RYZODEG 70/30 BID** previously on OD*/BID basal/premix/self-mix, ±OADs*** (N=279)
Severe hypoglycemia				
Percent of patients	0.4%	0%	3.1%	1.4%
Novo Nordisk hypoglycemia				
Percent of patients	49.8%	52.6%	66.1%	73.5%

*OD: once daily
**BID: twice daily
***OAD: oral anti-diabetic agent
[§]Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including RYZODEG 70/30 and may be life threatening *[see Warnings and Precautions (5.5)]*. Hypersensitivity (manifested with swelling of tongue and lips, diarrhea, nausea, tiredness and itching) and urticaria were reported in 0.5% of patients treated with RYZODEG 70/30.

Lipodystrophy

Long-term use of insulin, including RYZODEG 70/30, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy *[see Dosage and Administration (2.1)]*. In the clinical program, lipodystrophy was reported in 0.1% of patients treated with RYZODEG 70/30.

Injection Site Reactions

Patients taking RYZODEG 70/30 may experience injection site reactions, including injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection site mass. In the clinical program, injection site reactions occurred in 2.0% of patients treated with RYZODEG 70/30.

Weight Gain

Weight gain can occur with insulin therapy, including RYZODEG 70/30, and has been attributed to the anabolic effects of insulin. In the clinical program, patients with type 1 diabetes treated with RYZODEG 70/30 gained an average of 2.8 kg and patients with type 2 diabetes treated with RYZODEG 70/30 gained an average of 1.6 kg.

Peripheral Edema

Insulin, including RYZODEG 70/30, may cause sodium retention and edema. In the clinical program, peripheral edema occurred in 2.2% of patients with type 1 diabetes mellitus and 1.8% of patients with type 2 diabetes mellitus treated with RYZODEG 70/30.

6.2 Immunogenicity

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to RYZODEG 70/30 with the incidence of antibodies in other studies or to other products, may be misleading.

In studies of adult type 1 diabetes patients, 95.9% of patients who received RYZODEG 70/30 once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 89% that were positive at baseline, while 13% of these patients were positive for anti-IAsp antibodies at least once during the studies, including 6.4% who were positive at baseline. In studies of type 2 diabetes patients, 67.5% of patients who received RYZODEG 70/30 once daily were positive for AIA at least once during the studies, including 45.4% that were positive at baseline, while 17.1% of these patients were positive for anti-IAsp antibodies at least once during the studies, including 12.3% who were positive at baseline. The antibody incidence rates for type 2 diabetes may be underreported due to potential assay interference by endogenous insulin in samples in these patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper- or hypoglycemia.

The incidence of anti-insulin degludec antibodies has not been established.

7 DRUG INTERACTIONS

Table 5 includes clinically significant drug interactions with RYZODEG 70/30.

Table 5: Clinically Significant Drug Interactions with RYZODEG 70/30

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors.

Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of RYZODEG 70/30	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of RYZODEG 70/30	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine.
Intervention:	Increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with RYZODEG 70/30 or insulin degludec in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Available information from published randomized controlled trials with insulin aspart use during the second trimester of pregnancy have not reported an association with insulin aspart and major birth defects or adverse maternal or fetal outcomes *[see Data]*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal reproduction studies with insulin degludec/insulin aspart, visceral/skeletal abnormalities were observed with subcutaneous administration of insulin degludec/insulin aspart to pregnant rats during organogenesis at doses 8-times the human exposure at a subcutaneous dose of 1.08 units/kg/day. These effects were similar to those observed in rats administered human insulin (NPH) *[see Data]*.

Rats and rabbits were exposed to insulin degludec in animal reproduction studies during organogenesis. Pre-and post-implantation losses and visceral/skeletal abnormalities were observed in rats at doses 5 times (rat) and at 10 times (rabbit) the human exposure at a dose of 0.75 units/kg/day. These effects were similar to those observed in rats administered human insulin (NPH) *[see Data]*.

In animal reproduction studies, administration of subcutaneous insulin aspart to pregnant rats and rabbits during the period of organogenesis did not cause adverse developmental effects at exposures 8- times and equal to the human subcutaneous dose of 1.0 unit/kg/day, respectively. Pre- and post-implantation losses and visceral/skeletal abnormalities were seen at higher exposures, which are considered secondary to maternal hypoglycemia. These effects were similar to those observed in rats administered regular human insulin *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Human Data

Insulin aspart

Published data from 5 randomized controlled trials of 441 pregnant women with diabetes mellitus treated with insulin aspart starting during the late 2nd trimester of pregnancy did not identify an association of insulin aspart with major birth defects or adverse maternal or fetal outcomes. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including a variable duration of treatment and small size of the majority of the trials.

Animal Data

Insulin degludec/Insulin aspart

Subcutaneous reproduction and teratology studies have been performed with insulin degludec/insulin aspart, and human insulin (NPH) as a comparator in rats. In these studies, insulin degludec/insulin aspart was given to rats during organogenesis. The effect of insulin degludec/insulin aspart was consistent with those observed with human insulin as both caused visceral/skeletal abnormalities in rats at dose of 30 units/kg/day (approximately 8 times the

human exposure (AUC) at a human subcutaneous dose of 1.08 units/kg/day). The effects were likely due to maternal hypoglycemia.

Insulin degludec
Insulin degludec was investigated in studies covering fertility, embryo-fetal development and pre- and post-natal development in rats and during the period of embryofetal development in rabbits. Human insulin (NPH insulin) was included as comparator. In these studies insulin degludec caused pre- and post-implantation losses and visceral/skeletal abnormalities when given subcutaneously at up to 21 units/kg/day in rats and 3.3 units/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure (AUC) at a human subcutaneous dose of 0.75 units/kg/day. Overall, the effects of insulin degludec were similar to those observed with human insulin, which were probably secondary to maternal hypoglycemia.

Insulin aspart
Fertility, embryo-fetal and pre-and postnatal development studies have been performed with insulin aspart and regular human insulin in rats and rabbits. In a combined fertility and embryo-fetal development study in rats, insulin aspart was administered before mating, during mating, and throughout pregnancy. Further, in a pre- and postnatal development study insulin aspart was given throughout pregnancy and during lactation to rats. In an embryo-fetal development study insulin aspart was given to female rabbits during organogenesis. The effects of insulin aspart did not differ from those observed with subcutaneous regular human insulin. Insulin aspart, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 units/kg/day (approximately 32 times the human subcutaneous dose of 1.0 unit/kg/day, based on human exposure equivalents) and in rabbits at a dose of 10 units/kg/day (approximately three times the human subcutaneous dose of 1.0 unit/kg/day, based on human exposure equivalents). No significant effects were observed in rats at a dose of 50 units/kg/day and in rabbits at a dose of 3 units/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 unit/kg/day for rats and equal to the human subcutaneous dose of 1.0 unit/kg/day for rabbits, based on human exposure equivalents. The effects are considered secondary to maternal hypoglycemia.

8.2 Lactation

Risk Summary
There are no data on the presence of RYZODEG 70/30 or insulin degludec in human milk, the effects on the breastfed infant, or the effect on milk production. Insulin degludec is present in rat milk *[see Data]*. One small published study reported that exogenous insulin, including insulin aspart, was present in human milk. However, there is insufficient information to determine the effects of insulin aspart on the breastfed infant and no available information on the effects of insulin aspart on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for insulin, any potential adverse effects on the breastfed child from RYZODEG 70/30, insulin degludec or insulin aspart or from the underlying maternal condition.

Data

Insulin degludec
In lactating rats, insulin degludec was present in milk at a concentration lower than that in plasma.

8.4 Pediatric Use
The safety and effectiveness of RYZODEG 70/30 to improve glycemic control in type 1 and type 2 diabetes mellitus have been established in pediatric patients 1 year of age and older. The safety and effectiveness of RYZODEG 70/30 have not been established in pediatric patients less than 1 year old.

The use of RYZODEG 70/30 in pediatric patients 1 year of age and older with type 1 and type 2 diabetes mellitus is supported by evidence from an adequate and well-controlled study and a pharmacokinetic study (studies included pediatric patients 1 year of age and older with type 1 diabetes mellitus) *[see Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*. The use of RYZODEG 70/30 in pediatric patients 1 year of age and older with type 2 diabetes mellitus is also supported by evidence from adequate and well-controlled studies in adults with type 2 diabetes mellitus *[see Clinical Studies (14.3)]*.

In pediatric patients 1 year of age and older with switching from other insulin therapies, start RYZODEG 70/30 at a reduced dose to minimize the risk of hypoglycemia *[see Dosage and Administration (2.4, 2.5)]*.

8.5 Geriatric Use
In clinical studies *[see Clinical Studies (14)]* a total of 9 (2.5%) of the 362 RYZODEG 70/30-treated patients with type 1 diabetes were 65 years or older and 4 (1.1%) were 75 years and older. A total of 256 (25.7%) of the 998 RYZODEG 70/30-treated patients with type 2 diabetes were 65 years or older and 32 (3.2%) were 75 years and older. Differences in safety or effectiveness were not suggested in subgroup analyses comparing subjects older than 65 years to younger subjects.

Nevertheless, greater caution should be exercised when RYZODEG 70/30 is administered to geriatric patients since greater sensitivity of some older individuals to the effects of RYZODEG 70/30 cannot be ruled out. The initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be more difficult to recognize in the elderly.

8.6 Renal Impairment
In clinical studies *[see Clinical Studies (14)]* a total of 18 (5%) of the 362 RYZODEG 70/30-treated patients with type 1 diabetes had an eGFR less than 60 mL/min/1.73 m^2 or less and 1 (0.3%) had an eGFR less than 30 mL/min/1.73 m^2 or less. A total of 111 (11%) of the 998 RYZODEG 70/30-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m^2 and no subjects had an eGFR less than 30 mL/min/1.73 m^2.

No differences in the pharmacokinetics of the individual components of RYZODEG 70/30, insulin degludec or insulin aspart, were identified in separate studies comparing healthy subjects and subjects with renal impairment *[see Clinical Pharmacology (12.3)]*. However, as with all

insulin products, glucose monitoring should be intensified and the RYZODEG 70/30 dosage adjusted on an individual basis in patients with renal impairment.

8.7 Hepatic Impairment

No differences in the pharmacokinetics of the individual components of RYZODEG 70/30, insulin degludec or insulin aspart, were identified in separate studies comparing healthy subjects and subjects with hepatic impairment (mild, moderate, and severe hepatic impairment) *[see Clinical Pharmacology (12.3)]*. However, as with all insulin products, glucose monitoring should be intensified and the RYZODEG 70/30 dosage adjusted on an individual basis in patients with hepatic impairment.

10 OVERDOSAGE

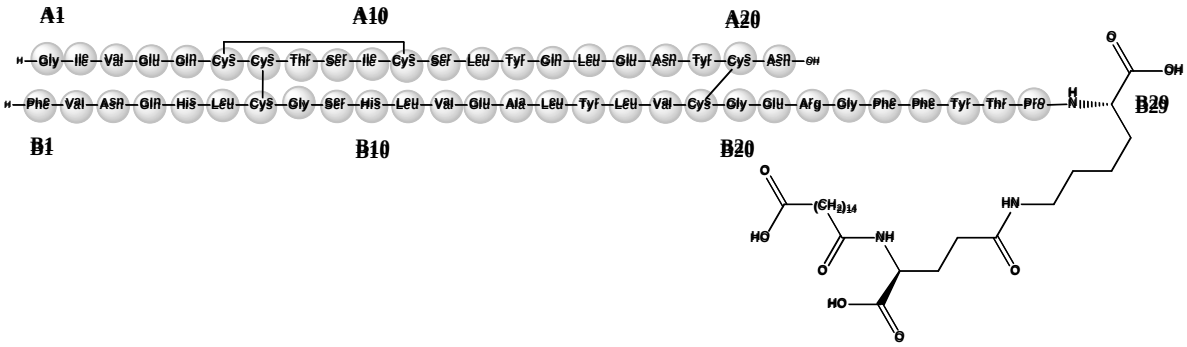
An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.6)]*. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

11 DESCRIPTION

RYZODEG 70/30 (insulin degludec and insulin aspart injection) is a human insulin analog solution containing 70% insulin degludec and 30% insulin aspart for subcutaneous injection. It consists of insulin degludec, a long-acting insulin, and insulin aspart, a rapid-acting insulin both of which function as parenteral blood-glucose-lowering agents *[see Clinical Pharmacology (12)]*.

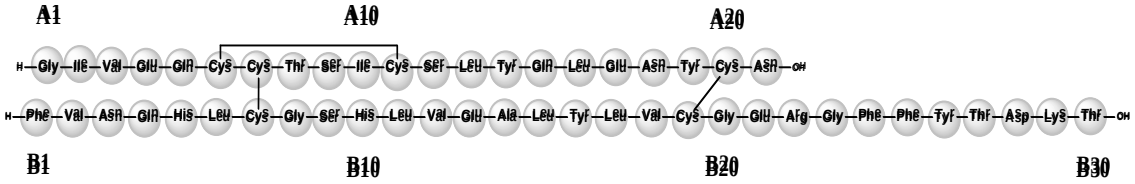
Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin) and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin degludec has a molecular formula of $C_{274}H_{411}N_{65}O_{81}S_6$ and a molecular weight of 6103.97.

Figure 1: Structural Formula of Insulin Degludec



Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin aspart has a molecular formula of $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

Figure 2: Structural Formula of Insulin Aspart



RYZODEG 70/30 is a sterile, aqueous, clear, and colorless solution and contains a total of 100 Units of insulin degludec and insulin aspart mixture per mL, glycerol 19 mg/mL, metacresol 1.72 mg/mL, phenol 1.50 mg/mL, sodium chloride 0.58 mg/mL, zinc 27.4 mcg/mL and water for injection. RYZODEG 70/30 has a pH of approximately 7.4. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

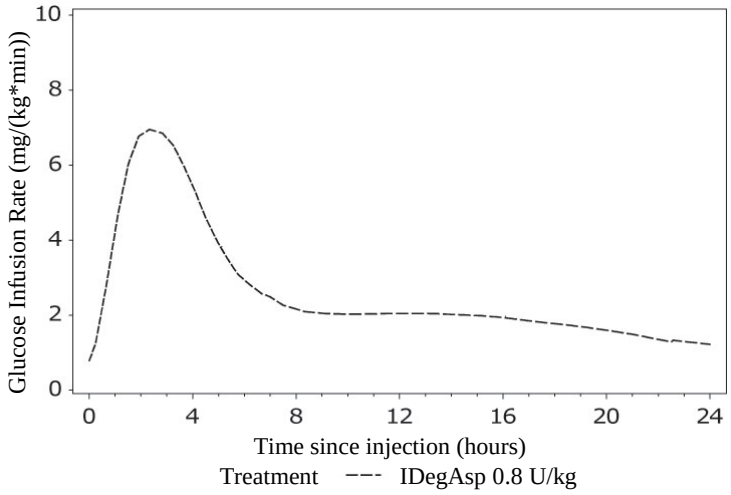
The primary activity of insulin, including RYZODEG 70/30, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis. The insulin degludec component in RYZODEG 70/30 forms multi-hexamers when injected into the subcutaneous tissue resulting in a subcutaneous insulin degludec depot. The protracted time action profile of RYZODEG 70/30 is predominantly due to delayed absorption of insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin. Insulin aspart monomers are released rapidly into the circulation.

12.2 Pharmacodynamics

The pharmacodynamic profile of RYZODEG 70/30 reflects the action profiles of rapid-acting insulin aspart and long-acting insulin degludec.

The pharmacodynamic profile for RYZODEG 70/30 given as single dose subcutaneous injections of 0.8 units/kg dose in a euglycemic clamp study in patients with type 1 diabetes, is shown in Figure 3. The mean maximum glucose lowering effect (GIR_{max}) of a 0.8 units/kg dose of RYZODEG 70/30 was 6.9 mg/kg/min, which was observed at a median of 2.3 hours post-dose.
In patients with type 1 diabetes mellitus and type 2 diabetes mellitus, RYZODEG 70/30 has an onset of action that rapidly follows injection. Basal insulin degludec in RYZODEG 70/30 provides a glucose lowering effect over 24 hours upon once-daily administration. The duration of action of a single-dose of RYZODEG 70/30 may extend beyond 24 hours (Figure 3) due to the presence of the basal component, insulin degludec.

Figure 3: GIR Profile of RYZODEG 70/30 After Single 0.8 units/kg Dose Administration in Patients with Type 1 Diabetes Mellitus



The total and maximum glucose-lowering effect of RYZODEG 70/30 increases linearly with increasing doses from 0.4 units/kg to 0.8 units/kg in patients with type 1 diabetes mellitus and type 2 diabetes mellitus. Steady-state background glucose-lowering, attributable to the long-acting, insulin degludec component, will occur after 3 to 4 days of dose administration. However, the magnitude of the glucose-lowering effect at steady-state is reduced in type 2 diabetic subjects in comparison to type 1 diabetic subjects given the same unit/kg RYZODEG 70/30 dose.

12.3 Pharmacokinetics

Absorption

The concentration-time profile following a single subcutaneous dose of 0.4, 0.6, and 0.8 units/kg RYZODEG 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus showed

increased exposure with increasing dose for both components of RYZODEG 70/30 (insulin degludec and insulin aspart).

Insulin aspart showed dose proportional increase in maximum concentration (C_{max}) and slightly more than dose proportional increase in overall exposure $AUC_{0\text{-}12h}$ following single subcutaneous administration of RYZODEG 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus.

Insulin degludec showed dose proportional increase in C_{max} and $AUC_{0\text{-}120h}$ following single subcutaneous administration of RYZODEG 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus.

The median onset of appearance for the insulin aspart component was 14 minutes after injection with a peak concentration after 72 minutes. Steady state serum concentrations of the insulin degludec component of RYZODEG 70/30 were reached after 3 to 4 days of dose administrations *[see Dosage and Administration (2.2)]*.

Distribution
The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. Insulin aspart has low binding to plasma proteins, <10%, similar to regular human insulin.

Elimination
The half-life after subcutaneous administration is determined primarily by the rate of absorption from the subcutaneous tissue. The half-life of the basal component (insulin degludec) at steady state is approximately 25 hours independent of dose. Degradation of insulin degludec is similar to that of human insulin. All metabolites formed are inactive.

Specific Populations

Pediatrics-
The total exposure of insulin aspart in RYZODEG 70/30 after a single subcutaneous dose (0.5 units/kg) did not show clinically relevant differences in children and adolescents compared to adults. Population pharmacokinetic analysis was conducted for insulin degludec using data from 224 pediatric subjects (1 to <18 years of age) with type 1 diabetes. Body weight was a significant covariate affecting clearance of insulin degludec. After adjusting for body weight, the total insulin exposure of insulin degludec at steady state was independent of age.

Geriatrics-
Pharmacokinetic and pharmacodynamic responses of RYZODEG 70/30 were investigated in 13 younger adult (18−35 years) and 15 geriatric (≥65 years) subjects with T1DM following two single s.c. dose administrations of 0.5 units/kg: one of RYZODEG 70/30 and one of NOVOLOG MIX 70/30. The total exposure of insulin aspart in RYZODEG 70/30 (based on $AUC_{IAsp,0\text{-}12h,SD}$) tended to be higher in geriatric subjects than in younger adult subjects. The total exposure of insulin degludec in RYZODEG 70/30 (based on $AUC_{IDeg,0\text{-}120h,SD}$) and the pharmacodynamic

response to RYZODEG 70/30 (based on $AUC_{GIR,0-24h}$) was similar in younger adult and geriatric subjects with T1DM, albeit higher between subject variability among the geriatric subjects.

Gender-
The effect of gender on the pharmacokinetics of the separate components of RYZODEG 70/30, insulin degludec and insulin aspart, was examined in across trial analyses of the pharmacokinetic and pharmacodynamic studies conducted using unit/kg doses of RYZODEG 70/30. Overall, there were no clinically relevant differences in the pharmacokinetic properties of insulin degludec or insulin aspart between female and male subjects.

Obesity-
The effect of BMI on the pharmacokinetics of the separate components of RYZODEG 70/30, insulin degludec and insulin aspart, was explored in cross-trial analyses of the pharmacokinetic and pharmacodynamic studies conducted using unit/kg doses of RYZODEG 70/30. For subjects with type 1 diabetes, there was no relationship between exposure of insulin degludec and BMI. For subjects with type 1 and type 2 diabetes, a trend for decrease in glucose-lowering effect of insulin degludec with increasing BMI was observed. For insulin aspart, there was no relationship between BMI and exposure in subjects with T1DM or T2DM.

Race and Ethnicity-
The effect of race and ethnic origin on the pharmacokinetics of RYZODEG 70/30 has not been studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a pharmacokinetic and pharmacodynamic study in Black or African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus conducted using unit/kg doses of insulin degludec. There were no statistically significant differences in the pharmacokinetic and pharmacodynamic parameters of insulin degludec between the racial and ethnic groups investigated.

Pregnancy-
The effect of pregnancy on the pharmacokinetics and pharmacodynamics of RYZODEG 70/30 has not been studied *[see Use in Specific Populations (8.1)]*.

Renal Impairment-
The effect of renal impairment on the pharmacokinetics of RYZODEG 70/30 has not been studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a pharmacokinetic study in 32 subjects (n=4-8/group) with normal or impaired renal function/end-stage renal disease following administration of a single subcutaneous dose (0.4 units/kg) of insulin degludec. Renal function was defined using creatinine clearance (Cl_{cr}) as follows: ≥90 mL/min (normal), 60-89 mL/min (mild), 30-59 mL/min (moderate) and <30 mL/min (severe). Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total ($AUC_{IDeg,0-120h,SD}$) and peak exposure of insulin degludec were on average about 10-25% and 13-27% higher, respectively, in subjects with mild to severe renal impairment, except subjects with ESRD, who showed similar exposure as compared to subjects with normal renal function. No systematic trend was noted for this increase in exposure across different renal impairment

subgroups. Hemodialysis did not affect clearance of insulin degludec ($CL/F_{IDeg,SD}$) in subjects with ESRD.

A single subcutaneous dose of 0.08 units/kg NOVOLOG (insulin aspart, the rapid-acting component of RYZODEG 70/30) was administered in a study to subjects with either normal, mild, moderate or severe (but not requiring hemodialysis) renal impairment. In this study, there was no apparent effect of creatinine clearance values on AUC and C_{max} of insulin aspart.

Hepatic Impairment-
The effect of hepatic impairment on the pharmacokinetics of RYZODEG 70/30 has not been studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a pharmacokinetic study in 24 subjects (n=6/group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a single subcutaneous dose (0.4 units/kg) of insulin degludec. No differences in the pharmacokinetics of insulin degludec were identified between healthy subjects and subjects with hepatic impairment *[see Use in Specific Populations (8.7)]*.

A single subcutaneous dose of 0.06 units/kg insulin aspart, the rapid-acting component of RYZODEG 70/30, was administered in an open-label, single-dose study of 24 subjects (n=6/group) with different degrees of hepatic impairment (mild, moderate, and severe). In this study, there was no correlation between the degree of hepatic failure and any insulin aspart pharmacokinetic parameter.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of insulin degludec/insulin aspart (RYZODEG 70/30).

In a 52-week study including human insulin (NPH insulin) as comparator, Sprague-Dawley rats were dosed subcutaneously with insulin degludec, the basal component of insulin degludec/insulin aspart (RYZODEG 70/30), at 3.3, 6.7, and 10 units/kg/day resulting in 5 times the human exposure (AUC) when compared to a human subcutaneous dose of 1.08 units/kg/day RYZODEG 70/30. Human insulin was dosed at 6.7 units/kg/day. No treatment-related increases in incidences of hyperplasia, benign or malignant tumors were recorded in female mammary glands from rats dosed with insulin degludec and no treatment related changes in the female mammary gland cell proliferation were found using BrdU incorporation. Further, no treatment related changes in the occurrence of hyperplastic or neoplastic lesions were seen in other tissues in animals dosed with insulin degludec when compared to vehicle or human insulin.

In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with insulin aspart, the rapid-acting component of insulin degludec/insulin aspart (RYZODEG 70/30), at 10, 50, and 200 units/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 units/kg/day, based on units/body surface area, respectively). At a dose of 200 units/kg/day, insulin aspart increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors found with insulin aspart was not significantly

different from that found with regular human insulin. The relevance of these findings to humans is not known.

Genotoxicity testing of insulin degludec was not performed. Insulin aspart was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and ex vivo UDS test in rat liver hepatocytes.

In a combined fertility and embryo-fetal study in male and female rats, treatment with insulin degludec up to 21 units/kg/day (approximately 5 times the human subcutaneous dose of 0.75 units/kg/day, based on units/body surface area) prior to mating and in female rats during gestation had no effect on mating performance.

In fertility studies with insulin aspart (NOVOLOG) in male and female rats, at subcutaneous doses up to 200 units/kg/day (approximately 32 times the human subcutaneous dose, based on units/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

14 CLINICAL STUDIES

The efficacy of RYZODEG 70/30 administered once-daily with the main meal of the day in adult and pediatric patients 1 year of age and older with type 1 diabetes and used with a mealtime insulin at remaining meals was evaluated in two randomized, open-label, treat-to-target, active-controlled trials. The efficacy of RYZODEG 70/30 administered once- or twice-daily with the main meal(s) in adults with type 2 diabetes when used with common oral anti-diabetic drugs was evaluated in four randomized, open-label, treat-to-target, active controlled trials.

Adult patients treated with RYZODEG 70/30 achieved levels of glycemic control similar to those treated with LANTUS (insulin glargine U-100) and LEVEMIR (insulin detemir) and NOVOLOG MIX 70/30 (biphasic insulin aspart 70/30). Pediatric patients treated with RYZODEG 70/30 achieved levels of glycemic control similar to those treated with LEVEMIR (insulin detemir).

14.1 Type 1 Diabetes – Adult

Study A: RYZODEG 70/30 Administered with the Main Meal in Combination with a Rapid-Acting Insulin Analog at Remaining Meals in Adult Patients

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 548 patients with type 1 diabetes mellitus inadequately controlled on either a basal-bolus regimen or other insulin regimens at baseline. Patients were randomized to RYZODEG 70/30 once-daily administered at the main meal of the day or insulin detemir once-daily at the evening meal or at bedtime. Insulin aspart was administered for the remaining insulin requiring meals. In patients randomized to insulin detemir, a second dose of insulin detemir could be added at breakfast after 8 weeks if glycemic control was inadequate.

The mean age of the trial population was 41.3 years and mean duration of diabetes was 17.4 years. 49.6% were male. 90.3% were White, 2.9% Black or African American. 3.1% were Hispanic. 4.8 % of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was 26.4 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and insulin detemir was -0.05% with a 95% confidence interval of [-0.18%, 0.08%] and met the pre-specified non-inferiority margin (0.4%). See Table 6.

Table 6: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Insulin Detemir in Adult Patients with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	RYZODEG 70/30 + Insulin aspart	**Insulin detemir* + Insulin aspart**
N	**366**	**182**
HbA_{1c} (%)		
Baseline	8.3	8.3
End of trial	7.6	7.6
Adjusted mean change from baseline [±]	-0.75	-0.7
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin detemir	-0.05 [-0.18;0.08]	
Proportion Achieving HbA_{1c} < 7% at Trial End	24.6%	20.3%
FPG (mg/dL)		
Baseline	186	198
End of trial	156	155
Adjusted mean change from baseline	-29.7	-33.8
Total Daily insulin dose**		
Baseline mean	56 U	56 U
Mean dose after 26 weeks	69 U	79 U

*Dosed once-daily or twice daily
**Total daily insulin dose includes basal and bolus insulin doses
[±]The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study A, there were 12.6% of subjects in RYZODEG 70/30 and 13.7% Insulin detemir arms for whom data was missing at the time of the HbA_{1c} measurement.

14.2 Type 1 Diabetes – Pediatric Patients 1 Year of Age and Older

Study F: RYZODEG 70/30 Administered with the Main Meal in Combination with a Rapid-Acting Insulin Analog at Remaining Meals in Pediatric Patients 1 Year of Age and Older

The efficacy of RYZODEG 70/30 was evaluated in a 16-week randomized, open-label, multi-national, multi-center trial in 362 patients with type 1 diabetes mellitus inadequately controlled on basal-bolus regimen or other insulin regimens at baseline. Patients were randomized to RYZODEG 70/30 once-daily administered at the main meal of the day or insulin detemir once- or twice-daily according to approved labeling. Subjects on an insulin detemir twice-daily regimen were dosed at breakfast and in the evening either with the main evening meal or at bedtime. Insulin aspart was administered for the remaining insulin requiring meals in the RYZODEG 70/30 treatment arm and for each insulin requiring meal in the insulin detemir treatment arm. At randomization it was recommended that the total daily insulin dose be reduced by 20% for both the treatment arms. At end of trial, 45.8% used insulin detemir once daily and 54.2% used insulin detemir twice daily.

The mean age of the trial population was 10.6 years; 22.7% were ages 1-5 years; 33.7% were ages 6-11 years and 43.6% were ages 12-17 years. The mean duration of diabetes was 4.1 years. 48.3% were male. 93.1% were White, 3.3% Black or African American. 7.7% were Hispanic. The mean z-score for body weight was 0.44.

At week 16, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and insulin detemir was -0.04% with a 95% confidence interval of [-0.23%, 0.15%] and met the pre-specified non-inferiority margin (0.4%). See Table 7.

Table 7: Results at Week 16 in a Trial Comparing RYZODEG 70/30 to Insulin Detemir in Pediatric Patients 1 Year of Age and Older with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	RYZODEG 70/30 + Insulin aspart	**Insulin detemir* + Insulin aspart**
N	182	180
HbA_{1c} (%)		
Baseline	8.1	8.1
End of trial	7.9	7.8
Adjusted mean change from baseline ±	-0.26	-0.22
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin detemir	-0.04 [-0.23; 0.15]	
FPG (mg/dL)		
Baseline	156	147
End of trial	154	152
Adjusted mean change from baseline	-0.8	-6.4

Total Daily insulin dose**		
Baseline mean	33 U (0.79 U/kg)	40 U (0.89 U/kg)
Mean dose after 16 weeks	38 U (0.88 U/kg)	46 U (1.01 U/kg)

*Dosed once-daily or twice-daily

**Total daily insulin dose includes basal and bolus insulin doses

±The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with missing data imputed by multiple imputation carrying forward the baseline value and adding an error term, with treatment, region, sex, and age group as fixed factors, and baseline HbA_{1c} as covariate.

In Study F, there were 4.9% of subjects in RYZODEG 70/30 and 8.3% Insulin detemir arms for whom data was missing at the time of the HbA_{1c} measurement.

14.3 Type 2 Diabetes – Adult

Study B: RYZODEG 70/30 Administered with the Main Meal as an Add-on to Metformin in Insulin Naïve Adult Patients

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 529 insulin-naïve patients with type 2 diabetes mellitus inadequately controlled on oral anti-diabetic drugs at baseline. Patients were randomized to RYZODEG 70/30 once-daily at breakfast or insulin glargine U-100 once-daily according to approved labeling. Metformin (Met) was administered in both arms.

The mean age of the trial population was 56.9 years and mean duration of diabetes was 9.2 years. 49.3% were male. 72.4% were White, 6.4% Black or African American. 21.6% were Hispanic. 4.5% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was 30.7 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and insulin glargine U-100 was 0.03% with a 95% confidence interval of [-0.14%, 0.20%] and met the pre-specified non-inferiority margin (0.4%). See Table 8.

Table 8: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Insulin Glargine U-100 in Insulin-Naïve Adult Patients with Type 2 Diabetes Mellitus

	RYZODEG 70/30 + Met	**Insulin glargine U-100 + Met**
N	**266**	**263**
HbA_{1c} (%)		
Baseline	8.9	8.9
End of trial	7.2	7.2
Adjusted mean change from baseline ±	-1.72	-1.75
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin glargine U-100	0.03 [-0.14;0.20]	
Proportion Achieving	45.9%	45.6%

HbA_{1c} < 7% at Trial End		
FPG (mg/dL)		
Baseline	183	187
End of trial	123	114
Adjusted mean change from baseline	-63.3	-72.5
Post Prandial Glucose (mg/dL)		
Prandial increment at breakfast, baseline	61	65
Prandial increment at breakfast, end of trial	34	62
Adjusted mean change from baseline	-27.2	-2.0
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin glargine U-100	-25.2 [-34.5; -15.9][1]	
Total Daily insulin dose		
Baseline mean	10 U	10 U
Mean dose after 26 weeks	66 U	59 U

[1] $p<0.001$, 1-sided p-value evaluated at 2.5% level for superiority

± The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study B, there were 17.7% of subjects in RYZODEG 70/30 and 12.9% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study C: RYZODEG 70/30 Administered with the Main Meal for Patients Inadequately Controlled on Once-Daily Basal Insulin and Oral Agents in Adult Patients

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 463 patients with type 2 diabetes mellitus inadequately controlled on basal insulin once-daily and oral antidiabetic drugs at baseline. Patients were randomized to RYZODEG 70/30 once-daily with either the evening meal or the largest meal of the day or insulin glargine U-100 once-daily according to approved labeling. The starting intervention insulin dose in units was determined by using the pre-trial basal insulin unit dose (1 to 1 unit conversion). The same oral anti-diabetic drugs were continued in both treatment arms which may have included any of the following used alone or in combination; Met, pioglitazone (Pio), DPP-4 inhibitors (DPP-4i) throughout the entire trial.

The mean age of the trial population was 58.1 years and mean duration of diabetes was 11.5 years. 56.6% were male. 56.4% were White, 8.0% Black or African American. 4.5% were Hispanic. 8.3% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was 30.1 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and insulin glargine U-100 was -0.03% with a 95% confidence interval of [-0.20%, 0.14%] and met the pre-specified non-inferiority margin (0.4%). See Table 9.

Table 9: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus

	RYZODEG 70/30 + Met ± Pio ± DPP-4i	**Insulin glargine U-100 + Met ± Pio ± DPP-4i**
N	**230**	**233**
HbA_{1c} (%)		
Baseline	8.3	8.4
End of trial	7.3	7.4
Adjusted mean change from baseline [±]	-1.00	-0.97
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin glargine U-100	-0.03 [-0.20;0.14]	
Proportion Achieving HbA_{1c} < 7% at Trial End	40.0%	36.5%
FPG (mg/dL)		
Baseline	144	141
End of trial	114	108
Adjusted mean change from baseline	-28.9	-34.9
Post Prandial Glucose (mg/dL)		
Prandial increment at dinner, baseline	48	55
Prandial increment at dinner, end of trial	22	46
Adjusted mean change from baseline	-32.3	-8.3
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin glargine U-100	-23.9 [-34.7;-13.0][1]	
Total Daily insulin dose		
Baseline mean	28 U	31 U
Mean dose after 26 weeks	60 U	60 U

[1] p<0.001, 1-sided p-value evaluated at 2.5% level for superiority

[±] The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex,

and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study C, there were 14.8 % of subjects in RYZODEG 70/30 and 12% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Type 2 Diabetes – Adult, BID

Study D: RYZODEG 70/30 Administered with the Main Meal for Patients Inadequately Controlled on Once-Daily or Twice-Daily Pre-Mix or Self-mixed Insulin in Adult Patients

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 446 patients with type 2 diabetes mellitus inadequately controlled on once- or twice-daily premixed or self-mixed insulin with or without background oral anti-diabetic agents. Patients were randomized to RYZODEG 70/30 or biphasic insulin aspart 70/30, both administered twice-daily before the breakfast and main evening meals. Subjects on premixed insulin twice-daily initiated trial insulin at the same dose as their premixed insulin (1 to 1 unit conversion). Subjects on a self-mixed regimen transfer to trial insulin at doses corresponding to their respective self-mixed pre-meal dose. Subjects previously receiving premixed or self-mixed insulin once-daily were to divide their dose into 2 equal doses. Patients continued on pre-trial oral background therapies which may have included any of the following used alone or in combination; Met, Pio, DPP-4i throughout the entire trial.

The mean age of the trial population was 58.7 years and mean duration of diabetes was 13.0 years. 55.6% were male. 52.5% were White, 0.2% Black or African American. 0.4% were Hispanic. 14.3% of patients had eGFR<60 mL/min/1.73 m^2. The mean BMI was 29.3 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and biphasic insulin aspart 70/30 was -0.03% with a 95% confidence interval of [-0.18%, 0.13%] and met the pre-specified non-inferiority margin (0.4%). See Table 10.

Table 10: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Biphasic Insulin Aspart 70/30 in Adult Patients with Type 2 Diabetes Mellitus

	RYZODEG 70/30 ± Met ± Pio ± DPP-4i	**Biphasic insulin aspart 70/30 ± Met ± Pio ± DPP-4i**
N	**224**	**222**
HbA_{1c} (%)		
Baseline	8.3	8.4
End of trial	7.1	7.1
Adjusted mean change from baseline [±]	-1.31	-1.29
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Biphasic insulin aspart 70/30	-0.03 [-0.18;0.13]	

Proportion Achieving HbA_{1c} < 7% at Trial End	50.4%	48.6%
FPG (mg/dL)		
Baseline	160	155
End of trial	104	123
Adjusted mean change from baseline	-50.4	-29.8
Total Daily insulin dose		
Baseline mean	54 U	51 U
Mean dose after 26 weeks	90 U	98 U

± The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study D, there were 12.1 % of subjects in RYZODEG 70/30 and 15.3% Biphasic insulin aspart 70/30 arms for whom data was missing at the time of the HbA_{1c} measurement.

Study E: RYZODEG 70/30 Administered with Any Main Meal for Patients Inadequately Controlled on Basal Insulin, Pre-Mix or Self-Mixed Insulin in Adult Patients

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 422 patients with type 2 diabetes mellitus inadequately controlled on basal insulin, premixed or self-mixed insulin in a once- or twice-daily insulin with or without background Met. Patients were randomized to RYZODEG 70/30 or biphasic insulin aspart 70/30, both administered twice-daily at the breakfast and main evening meal. Subjects on once-daily insulin split the total dose of their previous insulin treatment into 2 equal doses of trial insulin for twice-daily administration. Subjects on twice-daily insulin transferred their doses on a unit-to-unit basis to the trial insulin. Patients on Met continued Met at their pre-trial dose.

The mean age of the trial population was 59.8 years and mean duration of diabetes was 16.3 years. 54.5% were male. All patients were Asian. 17.2% of patients had eGFR <60 mL/min/1.73 m^2. The mean BMI was approximately 25.4 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and biphasic insulin aspart 70/30 was 0.05% with a 95% confidence interval of [-0.10%, 0.20%] and met the pre-specified non-inferiority margin (0.4%). See Table 11.

Table 11: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Biphasic Insulin Aspart 70/30 in Adult Asian Patients with Type 2 Diabetes Mellitus

	RYZODEG 70/30 ± Met	**Biphasic insulin aspart 70/30 ± Met**
N	**280**	**142**
HbA_{1c} (%)		
Baseline	8.4	8.4
End of trial	7.1	7.0
Adjusted mean change from	-1.39	-1.44

baseline [±]		
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Biphasic insulin aspart 70/30	0.05 [-0.10;0.20]	
Proportion Achieving HbA_{1c} < 7% at Trial End	48.2%	49.3%
FPG (mg/dL)		
Baseline	143	143
End of trial	97	116
Adjusted mean change from baseline	-45.3	-26.2
Total Daily insulin dose		
Baseline mean	37 U	37 U
Mean dose after 26 weeks	55 U	68 U

[±] The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study E, there were 12.1 % of subjects in RYZODEG 70/30 and 10.6% Biphasic insulin aspart 70/30 arms for whom data was missing at the time of the HbA_{1c} measurement.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RYZODEG 70/30 is as a clear and colorless solution available as a 3mL FlexTouch disposable prefilled pen (see Table 12).

Table 12 Presentations of RYZODEG 70/30

RYZODEG 70/30	Total volume	Concentration	Total units available in presentation	NDC number	Max dose per injection	Dose increment	Package Size
U-100 FlexTouch	3 mL	100 units/mL	300 Units	0169-2770-15	80 Units	1 Unit	5 pens/pack

16.2 Recommended Storage

Unused RYZODEG 70/30 should be stored between 36ºF to 46ºF (2ºC to 8ºC). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use RYZODEG 70/30 if it has been frozen.

Unopened FlexTouch disposable prefilled pen:
Not in-use (unopened) RYZODEG 70/30 disposable prefilled pen should be stored in a refrigerator 36ºF to 46ºF (2ºC to 8ºC). Discard after expiration date.

Open (In-Use) FlexTouch disposable prefilled pen:
The in-use RYZODEG 70/30 FlexTouch pen should be refrigerated (36ºF to 46ºF [2ºC to 8ºC]) or be kept at room temperature, below 86ºF (30ºC) away from direct heat and light. The opened (in-use) RYZODEG 70/30 FlexTouch pen may be used for up to 28 days (4 weeks) after being opened, if it is refrigerated or kept at room temperature.

The storage conditions are summarized in Table 13:

Table 13: Storage Conditions for RYZODEG 70/30 FlexTouch

	Not in-use (unopened)		In-use (opened)	
	Refrigerated (36^oF to 46^oF [2^oC to 8^oC])	**Room Temperature (below 86^oF [30^oC])**	**Room Temperature (below 86^oF [30^oC])**	**Refrigerated (36^oF to 46^oF [2^oC to 8^oC])**
3 mL RYZODEG 70/30 U100 FlexTouch	Until expiration date	28 days (4 weeks)	28 days (4 weeks)	28 days (4 weeks)

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

Never Share a RYZODEG 70/30 FlexTouch Pen Device Between Patients

Advise patients that they should never share a RYZODEG 70/30 FlexTouch pen device with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.1)]*.

Hyperglycemia or Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Inform patients of the symptoms of hypoglycemia. Inform patients that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Advise patients that changes in insulin regimen can predispose to hyper- or hypoglycemia. Advise patients that changes in insulin regimen should be made under close medical supervision *[see Warnings and Precautions (5.2)]*.

Medication Errors

Inform patients to always check the insulin label before each injection *[see Warnings and Precautions (5.4)]*.

Instruct patients that when injecting RYZODEG 70/30, they must press and hold down the dose button until the dose counter shows 0 and then keep the needle in the skin and count slowly to 6. When the dose counter returns to 0, the prescribed dose is not completely delivered until 6 seconds later. If the needle is removed earlier, they may see a stream of insulin coming from the needle tip. If so, the full dose will not be delivered, (a possible under-dose may occur by as much as 20%), and they should increase the frequency of checking their blood glucose levels and possible additional insulin administration may be necessary.

- If 0 does not appear in the dose counter after continuously pressing the dose button, the patient may have used a blocked needle. In this case they would **not** have received **any** insulin—even though the dose counter has moved from the original dose that was set.
- If the patient did have a blocked or damaged needle, instruct them to change the needle as described in Step 15 of the Instructions for Use and repeat all steps in the IFU starting with a new needle and the section Preparing your RYZODEG 70/30 FlexTouch Pen. **Make sure the patient selects the full dose needed.**

If patients routinely do not hold the needle under the skin as recommended, the patient may need to slightly increase the dialed insulin dose to achieve the patient's glycemic targets.

Instruct patients to not re-use needles. A new needle must be attached before each injection. Reuse of needles increases the risk of blocked needles which may cause under-dosing or overdosing.

Instruct Patients to never use a syringe to remove RYZODEG 70/30 from the FlexTouch disposable insulin prefilled pen.

Administration
RYZODEG 70/30 must only be used if the solution is clear and colorless with no particles visible.
Patients must be advised that RYZODEG 70/30 must NOT be diluted or mixed with any other insulin or solution *[see Dosage and Administration (2.1)]*.

Management of Hypoglycemia and Handling of Special Situations
Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals *[see Warnings and Precautions (5.3)]*.

Refer patients to the RYZODEG 70/30 "Patient Information" for additional information about the potential side effects of insulin therapy, including lipodystrophy (and the need to rotate injection sites within the same body region), weight gain, allergic reactions, and hypoglycemia.

Women of Reproductive Potential
Advise patients to inform their health care professional if they are pregnant or are contemplating pregnancy.

Rx Only

Date of Issue: 12/2016
Version: 3

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PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

For information about RYZODEG 70/30 contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

1-800-727-6500

www.novonordisk-us.com

Patient Information
RYZODEG® 70/30 (RY-zoh-deg)
(insulin degludec and insulin aspart injection)

Do not share your RYZODEG 70/30 FlexTouch delivery device with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is RYZODEG 70/30?

- RYZODEG 70/30 is a man-made insulin that is used to control high blood sugar in adults and children who are 1 year of age and older with diabetes mellitus.
- RYZODEG 70/30 is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- RYZODEG 70/30 is not for children who need less than 5 units of RYZODEG 70/30 each day.
- It is not known if RYZODEG 70/30 is safe and effective in children under 1 year of age.

Who should not take RYZODEG 70/30?

Do not take RYZODEG 70/30 if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to RYZODEG 70/30 or any of the ingredients in RYZODEG 70/30.

Before taking RYZODEG 70/30, tell your healthcare provider about all your medical conditions including, if you are:

- pregnant, planning to become pregnant, or are breastfeeding.
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

Before you start taking RYZODEG 70/30, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take RYZODEG 70/30?

- **Read the Instructions for Use** that come with your RYZODEG 70/30.
- Take RYZODEG 70/30 exactly as your healthcare provider tells you to.
- **RYZODEG 70/30 starts acting fast.** Inject RYZODEG 70/30 with your meal.
- If you take RYZODEG 70/30 1 time each day, take your dose with any main meal. If you take RYZODEG 70/30 2 times each day, take your dose with your 2 largest meals.
- Know the type and strength of insulin you take. **Do not** change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- If you miss or are delayed in taking a dose of RYZODEG 70/30:
  - Take your next dose with your next main meal on the same day and continue with your regular dosing schedule.
  - **Do not** take an extra dose.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- **Do not reuse or share needles with other people. You may give other people a serious infection or get a serious infection from them.**
- **Never** inject RYZODEG 70/30 into a vein or muscle.
- **Never** use a syringe to remove RYZODEG 70/30 from the FlexTouch pen.

What should I avoid while taking RYZODEG 70/30?

While taking RYZODEG 70/30 do not:

- Drive or operate heavy machinery, until you know how RYZODEG 70/30 affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of RYZODEG 70/30?

RYZODEG 70/30 may cause serious side effects that can lead to death, including:

- **Low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:
  - dizziness or light-headedness
  - sweating
  - confusion
  - fast heartbeat
  - blurred vision
  - slurred speech
  - shakiness
  - anxiety, irritability, or mood changes
  - hunger
  - headache
- **Low potassium in your blood (hypokalemia).**
- **Heart failure.** Taking certain diabetes pills called thiazolidinediones or "TZDs" with RYZODEG 70/30 may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure, it may get worse while you take TZDs with RYZODEG 70/30. Your healthcare provider should monitor you closely while you are taking TZDs with RYZODEG 70/30. Tell your healthcare provider if you have any new or worse symptoms of heart failure including shortness of breath, swelling of your ankles or feet, tiredness, sudden weight gain. Treatment with TZDs and RYZODEG 70/30 may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Your insulin dose may need to change because of:

- change in level of physical activity or exercise
- increased stress
- change in diet
- weight gain or loss
- illness

Common side effects of RYZODEG 70/30 may include:

- serious allergic reactions (whole body reactions), reactions at the injection site, skin thickening or pits at the injection site

(lipodystrophy), itching, rash, swelling of your hands and feet, and weight gain.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

These are not all the possible side effects of RYZODEG 70/30. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of RYZODEG 70/30.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about RYZODEG 70/30 that is written for health professionals. Do not use RYZODEG 70/30 for a condition for which it was not prescribed. Do not give RYZODEG 70/30 to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in RYZODEG 70/30?

Active Ingredient: 70% insulin degludec and 30% insulin aspart

Inactive Ingredients: zinc, metacresol, glycerol, phenol, sodium chloride, and water for injection. Hydrochloric acid or sodium hydroxide may be added.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark
For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration **Revised: 12/2016**

Instructions for Use

RYZODEG® 70/30 (RY-zoh-deg) FlexTouch® Pen 100 units/mL

(insulin degludec and insulin aspart injection)

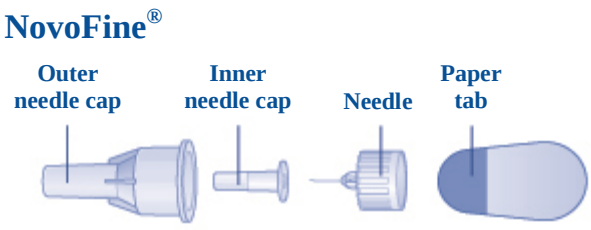
- **Do not share your RYZODEG 70/30 FlexTouch Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.**
- **RYZODEG 70/30 FlexTouch Pen 100 units/mL ("Pen") is a prefilled disposable pen** containing 300 units of RYZODEG 70/30 (insulin degludec and insulin aspart injection) 100 units/mL insulin. You can inject from 1 to 80 units in a single injection. The units can be increased by 1 unit at a time.
- **This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.**

Supplies you will need to give your RYZODEG 70/30 injection:

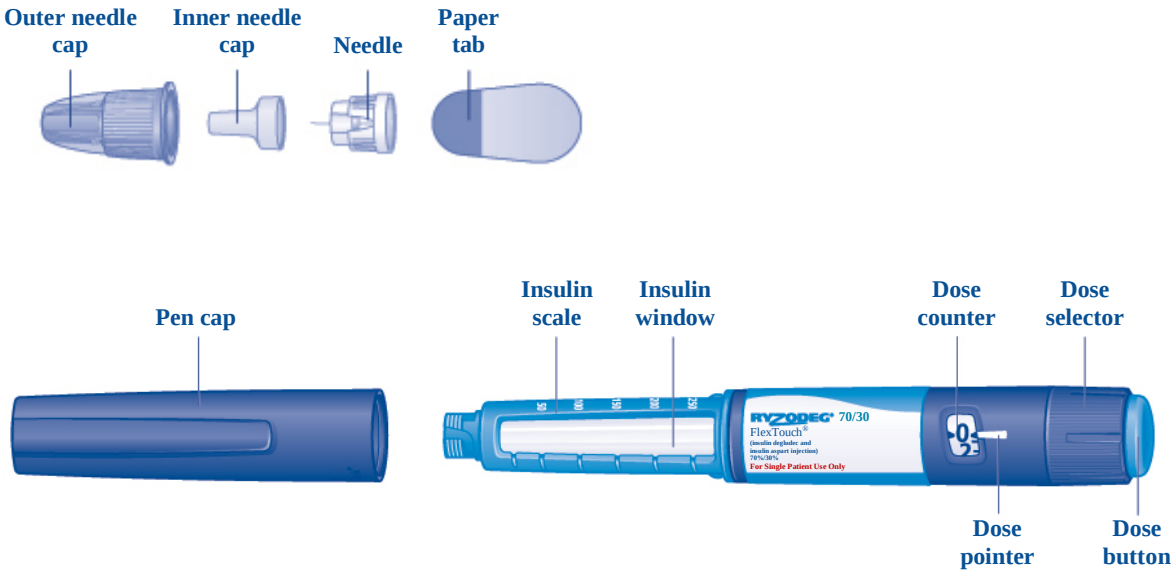
- RYZODEG 70/30 FlexTouch Pen
- a new NovoFine or NovoTwist needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. **See "After your injection" at the end of these instructions.**

Preparing your RYZODEG 70/30 FlexTouch Pen:

- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the RYZODEG 70/30 FlexTouch Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.**
- RYZODEG 70/30 should look clear and colorless. **Do not** use RYZODEG 70/30 if it is cloudy or colored.
- **Do not** use RYZODEG 70/30 past the expiration date printed on the label or 28 days after you start using the Pen.
- **Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.**



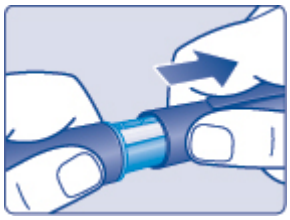
NovoTwist®



(Figure A)

Step 1:

• Pull Pen cap straight off (See Figure B).

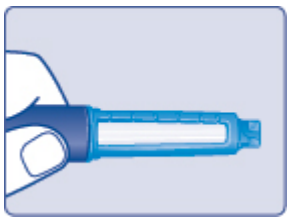


(Figure B)

Step 2:

• **Check the liquid in the Pen** (See Figure C). RYZODEG 70/30 should look clear and colorless.

Do not use it if it looks cloudy or colored.

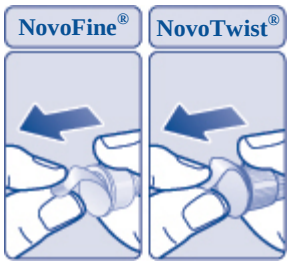


(Figure C)

Step 3:

• **Select a new needle.**

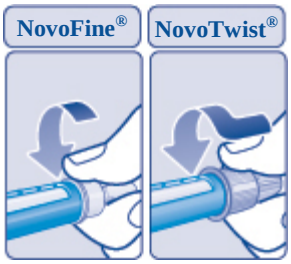
• Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

Step 4:

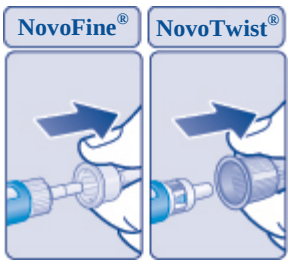
• Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

Step 5:

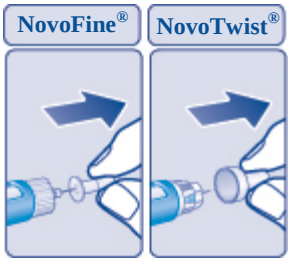
• Pull off the outer needle cap. **Do not** throw it away (See Figure F).



(Figure F)

Step 6:

• Pull off the inner needle cap and throw it away (See Figure G).

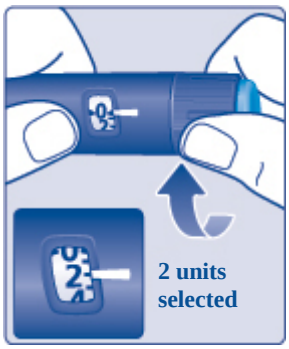


(Figure G)

Priming your RYZODEG 70/30 FlexTouch Pen:

Step 7:

• Turn the dose selector to **select 2 units** (See Figure H).



(Figure H)

Step 8:

• **Hold the Pen with the needle pointing up**. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).

(Figure I)

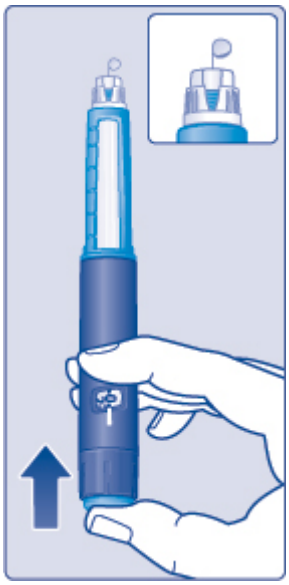
Step 9:

• **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows “0”. The “0” must line up with the dose pointer.

• A drop of insulin should be seen at the needle tip (See Figure J).

o If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.

o If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.



(Figure J)

Selecting your dose:

Step 10:

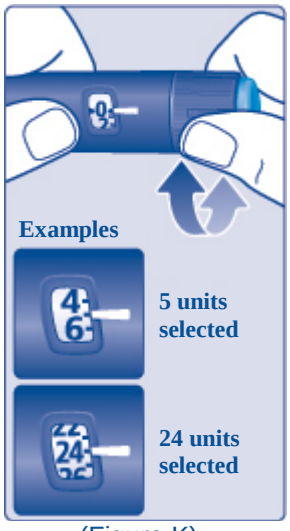
Check to make sure the dose selector is set at 0.

• **Turn the dose selector to select the number of units you need to inject.** The dose pointer should line up with your dose (See Figure K).

o If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.

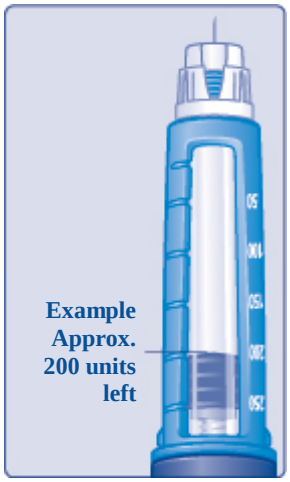
o The **even** numbers are printed on the dial.

o The **odd** numbers are shown as lines.



(Figure K)

• The RYZODEG 70/30 FlexTouch Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).



(Figure L)

• **To see how much insulin is left in your RYZODEG 70/30 FlexTouch Pen:**

o Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are **at least 80** units left in your Pen.

o If the dose counter shows **less than 80,** the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

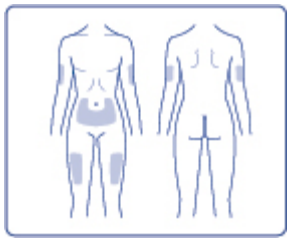
• Inject your RYZODEG 70/30 exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.

• RYZODEG 70/30 can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).

• Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

Step 11:

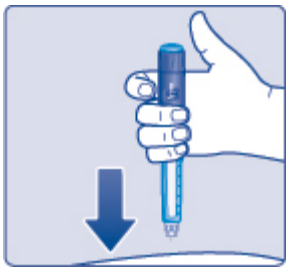
• Choose your injection site and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.


(Figure M)

Step 12:

• **Insert the needle into your skin** (See Figure N).

o **Make sure you can see the dose counter. Do not** cover it with your fingers, this can stop your injection.



(Figure N)

Step 13:

• **Press and hold down the dose button until the dose counter shows "0"** (See Figure O).

o The "0" must line up with the dose pointer. You may then hear or feel a click.

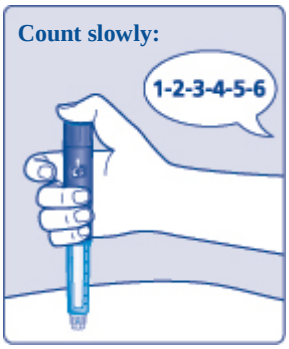
(Figure O)

• **Keep the needle in your skin after** the dose counter has returned to "0" and **slowly count to 6** (See Figure P).

o **When the dose counter returns to "0", you will not get your full dose until 6 seconds later.**

o **If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**

o **If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**

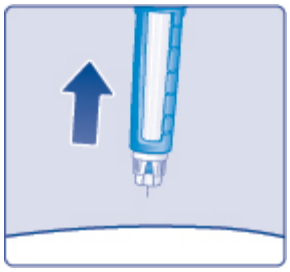


(Figure P)

Step 14:

• **Pull the needle out of your skin** (See Figure Q).

o If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.

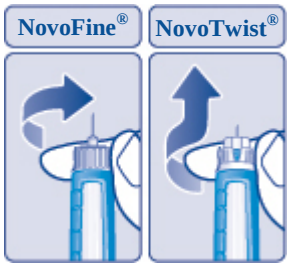


(Figure Q)

Step 15:

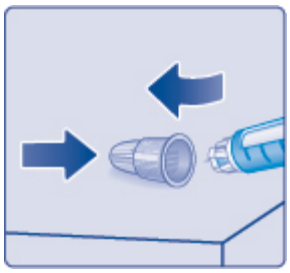
• **Carefully remove the needle from the Pen and throw it away** (See Figure R).

o **Do not** recap the needle. Recapping the needle can lead to needle stick injury.



(Figure R)

• If you **do not** have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.

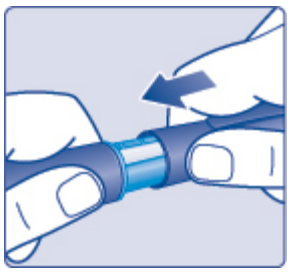


(Figure S)

o **Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

Step 16:

• Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

After your injection:

• Put your used RYZODEG 70/30 FlexTouch Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store my RYZODEG 70/30 FlexTouch Pen?

Before use:

- Store unused RYZODEG 70/30 FlexTouch Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).

- **Do not** freeze RYZODEG 70/30. **Do not** use RYZODEG 70/30 if it has been frozen.

- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.

Pen in use:

- Store the Pen you are currently using in the refrigerator between 36°F to 46°F (2°C to 8°C) or keep at room temperature below 86°F (30°C).

- Keep RYZODEG 70/30 away from heat or light.

- The RYZODEG 70/30 FlexTouch Pen you are using should be thrown away after 28 days if it is refrigerated or kept at room temperature, even if it still has insulin left in it and the expiration date has not passed.

General Information about the safe and effective use of RYZODEG 70/30.

- **Keep RYZODEG 70/30 FlexTouch Pens and needles out of the reach of children.**

- **Always** use a new needle for each injection.

- **Do not** share RYZODEG 70/30 FlexTouch Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

Revised: 12/2016

For information on how to use RyzoDeg 70/30 FlexTouch go to:
http://www.novotraining.com/ryzodeg7030flextouch/us01

For additional information about RyzoDeg 70/30 go to: www.ryzodeg7030.com